

72. (New) The method of claim 71, wherein the ligand is a single-chain antibody specific for the target protein.

73. (New) The method of claim 30, wherein the substrate comprises a plurality of adsorbent spots, each spot comprising the same adsorbent.

74. (New) The method of claim 30, wherein the substrate is a probe adapted for a desorption spectrometer which comprises adsorbents at different predetermined locations which are addressable by the energy source.

75. (New) The method of claim 30, wherein the substrate is in the form of a bead which is subsequently positioned on a probe adapted for a desorption spectrometer.

REMARKS

Status of the Application

Claims 30 and 33 are amended. Claims 25 and 26 are canceled, and claims 70-75 are added. Claims 30 and 33-75 are pending in this application. Claims 30, 33, 36, 42, 46, 49, 54, 58, 63, 64 and 67-69 have not been examined due to the election of species requirement. For the convenience of the Examiner, an appendix of pending claims is attached hereto.

The specification was objected to for the use of trademarks without proper designations. Claims 25, 30, 33 and 67-69 were rejected as allegedly being indefinite. Claims 25-26 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 11-20 of U.S. Patent No. 5,719,060. Claims 25-26 were rejected as allegedly being anticipated or as being obvious over either Hutchens *et al.* (WO94/28418) or Kauvar (WO89/09088). Claims 30, 33, 36, 42, 46, 49, 54, 58, 63, 64 and 67-69 were rejected as allegedly being obvious over Kauvar in view of Hillenkamp *et al.* (U.S. Pat. 5,118,937).

Support for the Amendment

Support for the amendments can be found throughout the specification, claims, and drawings, as originally filed. For example, support for amendments to claim 30 can be

found on, *e.g.*, page 34, lines 21 to page 37, line 20, page 67, lines 4-13 of the specification. Support for new claim 70 can be found on, *e.g.*, page 67, line 14 of the specification. Support for new claims 71 and 72 can be found on, *e.g.*, page 16, lines 9-15 of the specification. Support for new claim 73 can be found on, *e.g.*, page 29, line 25 of the specification. No new matter has been introduced. Support for new claim 74 can be found on, *e.g.*, page 27, line 16 of the specification. Support for new claim 75 can be found on, *e.g.*, page 28, lines 17-20 of the specification.

Election of Species

Applicants hereby affirm the election of peptides as the species for the adsorbent, the target analyte and the peptide library.

Applicants respectfully traverse the election of species requirement. Where claims can be examined together without undue burden, the Examiner must examine the claims on the merits even though they are directed to independent and distinct inventions. *See* MPEP §803.01. In the instant case, prosecution of all species would not place a substantially greater burden on the Examiner. Applicants therefore respectfully request that the Examiner withdraw the election of species requirement and consider all the claims together. Moreover, as indicated in the Office Action, upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. §1.141.

Information Disclosure Statement

Prior to issuance of the first Office Action (mailed December 8, 1999), Applicants filed three separate Information Disclosure Statements (IDS) and PTO Form 1449's (on September 30, 1998, January 14, 1999 and September 14, 1999). While Applicants received considered copies of the PTO Form 1449 for the IDS's filed on January 14 and September 14, 1999, Applicants have not yet received a considered copy of the PTO Form for the IDS filed on September 30, 1998.

During a telephone conference on June 6, 2000, Examiner Wessendorf stated that there is no record in the file that the U.S. Patent Office received the IDS filed September

30, 1998. Accordingly, Applicants herein submit copies of the IDS and PTO Form 1449 filed on September 30, 1998. Also enclosed is a stamped postcard returned from the U.S. Patent Office, indicating that Applicants filed the IDS. Applicants respectfully request the Examiner to consider the IDS and supply them with an initialed copy of the Form 1449, indicating that she has considered the documents cited thereon.

Applicants take this opportunity to apprise the Examiner of two other pending applications related to the present application. The present application, related U.S. application 09/100,708 and related U.S. application 09/100,302 have the same inventors (Hutchens and Yip), the same filing date, the same specification and claim the same chain of priority. They differ in having different claim sets. U.S. application 09/100,708 has been allowed.

Informalities

The specification was objected to for the use of the trademarks without appropriate notations and without an accompanying generic terminology. Applicants amended the specification to add proper notations and generic terminology for the trademarks. However, by doing so, Applicants do not admit that the terms are valid, registered trademarks. Withdrawal of the objection is respectfully requested.

Introduction

The claimed invention is directed to methods of screening agents for their ability to modulate binding between an immobilized molecule (called here an "adsorbent") and another molecule to which the adsorbent binds (called here a "target analyte"). The adsorbent can be, for example, a cell surface receptor protein for a hormone. The target analyte can be, for example, the hormone that binds to the cell surface receptor. The agent can be, for example, drug candidate being tested for the ability to inhibit binding between the receptor and the hormone. In one embodiment, the adsorbent is attached to the surface of a substrate. Then, it is exposed to the target analyte and to the agent under conditions that would ordinarily allow binding between the adsorbent and the target analyte. Then, the amount of target analyte bound to the adsorbent is tested by desorption spectrometry, a method in which energy is applied to the surface of the substrate to desorb and ionize the target analyte. The desorbed, ionized analytes are then detected by a detector. If the agent inhibits binding between the

adsorbent and the target analyte, then the amount of target analyte detected will be less than the amount detected if no agent were added. If the agent does not inhibit binding, then the amount of analyte detected will be the same as when no agent is added. In this way, one can screen the agents for possible drug candidates.

The 112, Second Paragraph, Rejection

Claims 25, 30, 33, 67-69 were rejected as allegedly being indefinite. Five grounds A)-E) of the rejection are separately addressed below.

Item A).

Claim 25 was rejected as allegedly being indefinite as to whether the adsorbent comprises a polypeptide. Applicants have canceled this claim in the interest of expediting the prosecution. Thus, the rejection is now moot.

Item B).

The Office Action states that the recitation in claim 25 of a polypeptide agent is inconsistent with the recitation of an "agent" in claim 30. Applicants have canceled claim 25 in the interest of expediting the prosecution. Thus, this rejection is now moot.

The Office Action questions whether "the adsorbent is made up of only a polypeptide or a polypeptide adsorbent with the attached or coated (polypeptide) agent. Applicants respectfully submit that as recited in dependent claim 42, "the adsorbent comprises a polypeptide." Thus, an adsorbent can consist of only a polypeptide or can include other materials.

The Office Action states that it is not clear as to how screening is done when the agent specifically reacts with the target analyte and suggests incorporating the limitation of claim 33 to claim 30. Applicants respectfully submit that the claim does not require that the agent "specifically reacts with the target analyte" as interpreted by the Examiner. Rather, the agent can bind to the target analyte, to the adsorbent, or to other molecules and modulate the binding between the target analyte and the adsorbent. Moreover, it is unclear to Applicants how incorporating the limitation of claim 33 to claim 30 would cure any alleged indefiniteness of the claim. Applicants respectfully request that this rejection be clarified in the next Office Action so that Applicants can further respond to the rejection if necessary.

Item C).

The Office Action states that the methods of screening a combinatorial library of agents in claim 33 broadens base claim 30.

Applicants respectfully traverse and submit that both claims 30 and 33 are clear and definite. Rather, the Examiner's rejection appears to be based on whether claim 33 meets the requirements of 35 U.S.C. §112, fourth paragraph, by further limiting the base claim. Applicants respectfully submit that dependent claim 33 does further limit independent claim 30. Specifically, claim 30 recites a method that comprises steps of screening an agent that modulates binding between a target analyte and an adsorbent. Since claim 30 uses open language "comprising", the method includes screening a single agent or a plurality of agents. Dependent claim 33 recites that a method is directed to screening a plurality of agents in a combinatorial library. Since claim 33 is limited to screening a plurality of agents, claim 33 further limits claim 30. Thus, claim 33 meets the requirements of 35 U.S.C. §112, fourth paragraph.

The Office Action further states that it is not clear whether the agents bind to the polypeptide present in the adsorbent or to the target analyte. Applicants respectfully submit that agents can bind either to the polypeptide present in the adsorbent or to the target analyte. For example, page 68, lines 20-23 of the specification states that "the proteins of a target cell type may be altered due to the action of the agent (*e.g.*, drug candidate) on 1) the target binding protein itself, 2) some other analyte (not the drug binding protein)...." This and other passages in the specification clearly support that an agent can modulate binding between an adsorbent and a target analyte in a number of ways.

Item D).

The Office Action states that "[t]he method step of claim 33(b) is confusing as to the exclusive binding of the target analyte and the adsorbent *i.e.*, to the exclusion of the agent (the polypeptide agent?) and adsorbent binding." Initially, Applicants note that claim 30, not claim 33, recites step (b). Specifically, claim 30, step (b), as amended, recites "exposing the substrate to the target analyte and to the agent under elution condition that allows binding between the target analyte and the adsorbent." (Emphasis added). This amendment clarifies that the binding does not refer to the exclusive binding of the target analyte and the adsorbent.

Rather, it refers to the elution condition. That is, the elution condition is selected so that it allows binding between the target analyte and the adsorbent (*e.g.*, in the absence of an agent). When the agent is added under that elution condition, it may bind to the target analyte, the adsorbent, or other molecules, and modulate the binding between the adsorbent and the target analyte. Thus, the claim is definite.

Item E).

The Office Action objects the use of the term “whereby”, because the term is allegedly “superfluous and merely provides for confusion as to the intent of said term, within the claimed context.” Applicants disagree. However, to expedite the prosecution, Applicants have deleted the term “whereby.” Thus, the rejection is now moot.

For the above reasons, the claims are definite. Accordingly, withdrawal of the indefiniteness rejection is respectfully requested.

The Obviousness-type Double Patenting Rejection

Claims 25-26 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 11-20 of U.S. Patent No. 5,719,060.

In the interest of expediting the prosecution, Applicants have canceled claims 25 and 26. Thus, the rejection is now moot.

The Rejection under 35 U.S.C. 102(b) and/or 103

Claims 25 and 26 were rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternatively, under 35 U.S.C. 103(a) as obvious over either Hutchens *et al.* (WO94/28418) or Kauvar (WO89/09088).

In the interest of expediting the prosecution, Applicants have canceled claims 25 and 26. Thus, the rejection is now moot.

The Rejection under 35 U.S.C. 103

Claims 30, 33, 36, 42, 46, 49, 54, 58, 63-64 and 67-69 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Kauvar in view of Hillenkamp *et al.* (U.S. Pat. 5,118,937).

As an initial matter, it is noted that the Office Action does not indicate which Kauvar reference (*i.e.*, WO89/09088, WO89/03430, U.S. Pat. 5,599,901, U.S. Pat. 5,541,070, U.S. Pat. 5,356,784, U.S. Pat. 5,340,474, U.S. Pat. 5,338,659, U.S. Pat. 5,133,866, or U.S. Pat. 4,963,263) is being applied in this rejection. Since the Office Action refers to Kauvar (WO89/09088) in the rejection under 35 U.S.C. §102, Applicants assume that the same Kauvar reference is being applied in the instant rejection. If this assumption is incorrect, Applicants respectfully request clarification as to which Kauvar reference is being relied upon.

At pages 11-12 of the Office Action, the Examiner states the following:

Kauvar discloses a method of screening a polypeptide agent that modulates binding between a target analyte and adsorbent comprising reacting the substrate to the target analyte and detecting an amount of binding between the target analyte and adsorbent containing polypeptide and measuring the amount of binding in the presence or absence of a modulating agent except the measurement of binding is not done by desorption spectrometry, as recited. However, Hillenkamp discloses the advantages derived in the use of a desorption spectrometry for large biomolecules. *See* page 11 of the Office Action.

Then the Examiner concludes that the claimed invention is obvious in view of Kauvar and Hillenkamp.

Applicants respectfully traverse this rejection. First, obviousness has not been established, because the cited references, alone or in combination, do not teach or suggest all the limitations of the claims. Second, there is no motivation to combine the references in the manner suggested by the Examiner. Third, improper hindsight was used to combine the references.

A. Kauvar and Hillenkamp Do Not Teach or Suggest All the Claimed Limitations

Obviousness has not been established, because Kauvar and Hillenkamp, alone or in combination, do not teach or suggest all the limitations of the claims. To establish *prima facie* obviousness, all of the claim limitations must be taught or suggested by the prior art. *In re Ryoka*, 180 USPQ 580 (CCPA 1974). *See, also*, MPEP §2143.03. In the instant case, Kauvar does not teach or suggest a method including, *inter alia*, “determining whether the agent modulates binding by comparing the measured amount of binding between the target

analyte and the adsorbent in the presence of the agent and a control amount of binding between the target analyte and the adsorbent without the presence of the agent” as recited in claim 30. As recited in this step, the claimed invention generally relates to a screening method for an agent and determining whether the agent modulates binding between a pair of elements, *i.e.*, a target analyte and an adsorbent. By contrast, Kauvar is not performing this step. Rather, Kauvar is simply experimenting to determine whether a paralog binds to an analyte of interest. *See, e.g.*, the section titled “Disclosure of the Invention” at pages 5-6 of Kauvar.

It may be that the Examiner is relying on the section in Kauvar titled “Screening Procedures” for paralogs in rejecting the claims. The Examiner appears to believe that the “paralog” in Kauvar meets the “adsorbent” limitation in the claim. This section relates to screening procedures to determine which paralog of many paralog candidates is the most favorable for binding an analyte of interest (*see, e.g.*, page 13, lines 6-23 of Kauvar). According to page 13, lines 20-23 of Kauvar, “[b]y assessing the ability of the analyte to compete, those paralogs which show the greatest decrease in label uptake are selected as having parameters that are most favorable for binding [the] analyte.” Thus, it appears that Kauvar is determining *which of a plurality of candidate paralogs on a panel is most favorable for binding an analyte*. Kauvar is not determining whether an agent modulates binding between an analyte and a paralog.

Moreover, the step of determining whether an agent modulates binding between the target analyte and the adsorbent, in conjunction with other recited steps, is not obvious in view of Kauvar. According to the Examiner, “Kauvar discloses a method of screening a polypeptide ‘agent’ that modulates binding between a target analyte and adsorbent.” *See* page 11 of the Office Action. Contrary to this characterization, the polypeptide agents are not screened in Kauvar. For example, as explained at page 12, lines 28-30 of Kauvar, “it may be necessary in utilizing the labeled peptide mixture to verify that *satisfactory binding occurs* with regard to all candidate paralogs in a panel.” (Emphasis added). Thus, the interaction (*i.e.*, binding) of paralogs and the peptides in Kauvar is known. However, in embodiments of the invention, the interaction between the adsorbents and the agent is not as pertinent. Rather, it is whether the agent has the ability to modulate (*e.g.*, interfere or promote) the interaction of the adsorbent and the target analyte. Consequently, there is no teaching or suggestion in Kauvar to

“screen” polypeptides as alleged, let alone desorb them for analysis using desorption spectrometry. If anything is “screened” in Kauvar, it is the paralogs. *See, e.g.*, page 10, lines 11-14 of Kauvar.

These deficiencies of Kauvar are not cured by Hillenkamp. Hillenkamp relates to a process for the laser desorption of analyte molecular ions from a specimen. There is no teaching or suggestion in Hillenkamp, *inter alia*, of any screening or comparing step as recited in step (d) of claim 30. Thus, Hillenkamp does not cure the deficiencies of Kauvar.

B. No Motivation to Combine the Cited References

Obviousness has not been established, because there is no motivation to combine the references in the manner suggested by the Examiner. A proper obviousness rejection requires, *inter alia*, that the prior art suggest making the claimed invention. The suggestion must be found in the prior art, not in Applicant’s disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). The Court of Appeals for the Federal Circuit has recently reviewed and restated the longstanding prohibition against the PTO’s use of an applicant’s disclosure as a recipe from which to choose references that describe each of the ingredients:

Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. *See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing “teaching or suggestion or motivation [to combine]” as an “essential evidentiary component of an obviousness holding”). *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

The Court stated that “actual evidence” of a motivation to combine references is required, “[t]hat is, the showing must be clear and particular. *See, e.g., C.R. Bard*, 157 F.3d at 1352, 48 USPQ2d at 1232. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not ‘evidence.’” *Id.*

Applicants respectfully traverse the rejection and submit that the instant rejection does not satisfy this requirement of providing actual evidence of a motivation to combine references. More particularly, there is no teaching or suggestion in the cited references for using Hillenkamp’s laser desorption spectrometry in Kauvar’s methods for

screening candidate paralogs, as alleged by the Examiner. In determining whether an analyte binds to a paralog, Kauvar describes in his example using a radiolabel and detecting binding using an X-ray film or a gamma counter. *See* page 17, line 35 to page 18, line 5 of Kauvar. Nothing in Kauvar suggests that desorption spectrometry would be useful in detecting and quantitating analytes in screening methods. Nothing in Hillenkamp suggests that using desorption spectrometry would be useful for screening assays. Therefore, an allegation that it would have been obvious to combine the methods of Kauvar with those of Hillenkamp "for the advantage disclosed by Hillenkamp" is merely a broad conclusory statement, and is not the "actual evidence" of motivation as required by the law. Accordingly, there is no motivation to combine the references in the manner suggested by the Examiner.

C. Improper Hindsight Used

Finally, obviousness has not been established, because absent hindsight, the skilled artisan would not have modified Kauvar in view of Hillenkamp in the manner suggested by the Examiner. As described above, there is no motivation to combine Kauvar and Hillenkamp. Thus, the Examiner must have necessarily used hindsight in combining the references. As explain in MPEP §2141.01:

Requirement for "at the time the invention was made" is to avoid impermissible hindsight... "It is difficult but necessary that the decisionmaker forget what he or she taught ... about the claimed invention and cast the mind back to the time the invention was made ***", to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). (Emphasis added).

The only place of record that provides the desirability of using desorption laser spectrometry in combination with the other claim element is the present specification. The Examiner necessarily had to look at Applicants' own specification to arrive at the invention. Since the Examiner has not established that one viewing only the references cited in the rejection would have been led to arrive at the claimed invention, without looking at Applicants' specification, the rejection is improper.


For the above reasons, a *prima facie* case of obviousness has not been established. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415)576-0200.

Respectfully submitted,


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